Scientific Abstract

Malignant melanoma is a neoplastic disorder of melanocytes, a pigment producing cell type derived from neural crest cells. Patients with advanced malignant melanoma have a poor prognosis, respond poorly to conventional therapy, and are appropriate candidates for experimental approaches to treatment. Patients with malignant melanoma appear to have weak, but measurable, immune responses to melanoma. Immunotherapy with biologic response modifiers such as interleukin-2 and interferon-α, or adoptive transfer of T-lymphocytes, is associated with significant disease response in a subset of patients. Important limitations to the current effectiveness of immunotherapy for melanoma include the low baseline frequency of melanoma reactive lymphocytes, tumor induced immune suppression, and defects in the function of lymphocytes expanded *ex vivo* for adoptive immunotherapy. Experimental evidence suggests that targets of the cellular immune response to melanoma include the melanocyte lineage antigens MART-l, MAGE-1 and MAGE-3, gp100, and tyrosinase. Many of these antigens were defined through the isolation of MHC Class I restricted, CD8$^+$ T-cell clones capable of eliciting melanoma specific anti-tumor responses. Characterization of potential antigenic targets has suggested new avenues to amplify specific immune responses to melanoma, as well as the means to quantitatively monitor the immunologic response to treatment. We have developed a novel approach to adoptive immunotherapy for melanoma based on genetic modification of activated autologous T-cells. The cDNAs encoding the α-chain and β-chain of a MHC Class I restricted, MART-l (m27-35) specific T-cell receptor were cloned into a bicistronic retroviral expression vector developed in our laboratory. Using a novel, clinically applicable viral transduction protocol, we are able to efficiently transduce activated T-lymphocytes. Both CD4$^+$ and CD8$^+$ T-cells express the Class I restricted TCR following retroviral gene transfer. Genetically modified T-cells exhibit antigen specific cytotoxicity and Th1-like cytokine release when challenged with MART-1 peptide presented by HLA-A2. In this application, we propose a clinical trial to evaluate the safety, function, and anti-tumor activity of these genetically modified T-cells following adoptive transfer in patients with advanced melanoma. A Phase I dose escalation study of genetically modified T-cells will be performed without and with systemic recombinant human interleukin-2 (rhIL-2) in HLA-A2$^+$ patients with advanced melanoma. The primary endpoint of the study is determination of the maximal tolerated dose of MART-l specific T-cells in the presence and absence of rhIL-2. Secondary endpoints include measurement of the *in vivo* survival and function of genetically modified T-cells, and assessment of patients for antitumor response. This trial will provide important information on the safety, utility, and potential limitations of using gene transfer to engineer immune responses to tumor rejection antigens, and will form the basis of subsequent clinical trials designed to test the therapeutic benefit of this novel approach to cancer treatment.